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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/614,037	07/08/2003	Manfred Reiter	14693-0195	9074
<div>61263 7590 01/28/2008</div> <div>PROSKAUER ROSE LLP</div> <div>1001 PENNSYLVANIA AVE, N.W.,</div> <div>SUITE 400 SOUTH</div> <div>WASHINGTON, DC 20004</div>				
			<div>EXAMINER</div> <div>VOGEL, NANCY S</div>	
			<div>ART UNIT</div> <div>1636</div>	<div>PAPER NUMBER</div>
			<div>MAIL DATE</div> <div>01/28/2008</div>	<div>DELIVERY MODE</div> <div>PAPER</div>

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/614,037

Applicant(s)

REITER ET AL.

Examiner

Nancy T. Vogel

Art Unit

1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 31 October 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 34-36, 46-66 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 34-36 and 46-66 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 34-36 and 46-66 are pending in the case.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/07 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 49, 52, 60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification as originally filed does not provide support for the invention as now claimed: "wherein the infected cells are incubated in an animal protein free culture

medium comprising at least one hydrolysate selected from the group consisting of a soy hydrolysate and a yeast hydrolysate" (49), and "where the virus is propagated in an animal protein free culture medium comprising at least one hydrolysate selected from the group consisting of a soy hydrolysate and a yeast hydrolysate" (52), "wherein the infected culture of cells are cultivated in an animal protein free culture medium comprising at least one hydrolysate selected from the group consisting of a soy hydrolysate and a yeast hydrolysate" (6), since the specification discloses only the growth medium comprising both yeast and soy hydrolysate. This a new matter rejection. The specification does not provide sufficient blazemarks nor direction for the instant methods encompassing the above-mentioned limitations, as currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Claims 34-36, 46-66 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention: The invention is drawn to a method of producing immunogenic composition comprising a virus or a virus antigen, comprising growing cultures of cells in an animal protein free medium comprising soy hydrolysate and yeast hydrolysate.

The state of the prior art: The prior art disclosed methods of cell culture comprising soy and yeast hydrolysate, and also generally include the addition yeast and/or soy hydrolysates, and in some disclosures, animal protein components, either in the form of undefined serum additives, or particular animal proteins in defined form. Cell culture techniques generally are the result of trial and error experimentation.

The level of predictability in the art: The prior art in methods of cell culture and media appropriate for cell growth is unpredictable, and appears to be a matter of trial and error experimentation. Shibuya et al. (US Patent 6,406,909) disclose a method of growth of cells in basal media comprising soy and yeast hydrolysates that meet the limitations of the claims; however, as acknowledged by applicant in the response of 1/31/07, Shibuya et al. disclose that growth of the cells required the addition of a protein

which is recombinantly-produced insulin (page 8-9). Therefore, Shibuya et al. discloses the exact conditions disclosed by applicant, and yet, cell growth or maintenance was not supported under those conditions. Therefore, it is clear that the field is unpredictable, and that it cannot be predicted whether any particular type of culture media, will successfully support the growth of any cell type as claimed by applicant.

Breadth of the claims: The claims are very broad, since some are drawn to a method of cell producing any immunogenic composition comprising any virus or any virus antigen, using any cell type, grown with any "animal protein free medium", with the only proviso being that soy and yeast hydrolysate are present in certain concentrations and have components with a molecule weight of less than 100 Daltons.

Amount of guidance: The amount of guidance provided is small, since it is only stated in the specification that any "basal" medium may be used.

Existence of working examples: The specification discloses VERO cells, grown with one type of medium, i.e. basal DMEM/HAM's F12(1:1) medium supplemented with "inorganic salts, amino acids, vitamins and other components", in addition to "sodium bicarbonate...L-Glutamine" and soy and yeast hydrolysates (page 17).

Quantity of experimentation: In the absence of appropriate guidance for the full scope of the claims, and the unpredictability in the art, the quantity of experimentation needed to practice the invention as claimed would be extensive, since one would have to use trial and error experimentation to determine the type of cell culture needed to culture any particular cell type. It remains possible that the claimed methods would not

support culture of some cell types, as evidenced by Shibuya et al. No guidance regarding this matter is disclosed in the specification.

Claim Rejections - 35 USC § 103

Claims 34-36 and 46-66, are rejected under 35 U.S.C. 103(a) as being unpatentable over Price et al. (WO 98/15614) in view of Kistner et al. (US Patent 5,753,489), Luderer et al. (US P patent 4282315), Gauri et al. (US Patent 4,322,404) and Quest International Product Information, Norwich NY, 1995, and Sheffield Pharma Ingredients, Cell Nutrition, Hydrolyzed Proteins & Yeast Extracts, Technical Manual (all previously cited).

This rejection is maintained for the reasons made of record in the previous office action, 10/18/07, with slight modification necessitated by applicant's amendments to the claims.

Price et al. disclose a method of culturing cells comprising providing a culture of cells that have been grown in an animal protein free medium comprising soy hydrolysate at a concentration of about .1% and/or yeast hydrolysate at a concentration of 0.1% to about .8% (pages 19-20) . Price et al. disclose this method is useful for culture of animal cells including human cells and kidney cells (see page 24). Price disclose the method may be used to grow and produce viruses using cell culture (page 2).

The difference between the reference and the instant claims is that the steps of infecting the cells with virus, incubating the infected cells to propagate the virus,

harvesting the virus and preparing an immunogenic composition, and specifically, conducting those steps using particular viruses, is not disclosed. Furthermore, purifying said virus or antigen by ion exchange or gel filtrations is not disclosed. Furthermore, particular sizes of the molecules in the hydrolysates, i.e. 90% of the molecules in the hydrolysates have a molecule weight of less than or equal to 1000 Daltons, is not disclosed.

However, Kistner et al. disclose a method of producing an immunogenic composition comprising virus or virus antigen, comprising providing a culture of a mammalian cells, infecting the cells with a virus, incubating the culture of cells to propagate the virus, harvesting the virus or antigen, and preparing an immunogenic composition from the virus or antigen (see col. 5-6). The virus may be orthomyxoviridae, paramyxoviridae and reoviridae, and the cells may be vertebrate cells such as VERO, CV-1, LLC-MK2, MDCK, MDBK cells (col. 6, lines 1-15). Luderer et al. and Gauri et al. disclose the purification of virus by such well known techniques as gel filtration (col. 2 line 55-70 of Luderer et al.; see col. 3, lines 5-15 of Gauri et al.). Quest International Product Information discloses that HY-SOY, which is a well known soy hydrolysate, has 25.4% of molecules less than 200 D, 57.5% in the 200-500 D range, and 16.8% in the 500-1000 D range. The product pages disclose that the hydrolysates are useful for applications that require high solubility, including microbiological laboratories and in fermentation products requiring a water soluble, vegetable source peptone.. . Furthermore, technical literature from Sheffield Pharma, current makers of

such products as "Hy-Soy"TM and "Hy-Yest"TM also show that the molecular weight distribution of virtually all products is: 90% of molecules are less than 1 kD in size.

It would have been obvious to one of ordinary skill in the art to have included the steps of infecting the cultured cells with a virus of interest, cultivating the infected cells, harvesting the virus, and isolating an immunogenic antigen therefore, as disclosed by Kistner et al., in the method of cultivating cells disclosed by Price et al., since both references disclose the growth of cells in culture for the purpose of producing virus or recombinant products of interest. It would have been further obvious to use well known soy or yeast hydrolysates commercially available, such as those disclosed in the Quest International Product Information pages, which are disclosed to be "refined" and to have a molecule weight distribution in which at least 90% of the molecules have a molecule weight of less than or equal to 1000 Daltons. Furthermore, technical literature from Sheffield Pharma, current makers of such products as "Hy-Soy"TM and "Hy-Yest"TM also show that the molecular weight distribution of virtually all products is: 90% of molecules are less than 1 kD in size. One would have been motivated to do so by the disclosure of Price et al. that the method avoids contamination by animal proteins, and the usefulness of the cell culture method for producing virus, and the disclosure of the Quest International product information, which discloses that the hydrolysates are refined and are of low molecular weight, and are useful for applications that require high solubility, including microbiological laboratories and in fermentation products requiring a water soluble, vegetable source peptone.. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the

contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Applicant's arguments filed 10/31/07 have been considered but have not been found convincing. Applicant has argued that Price et al. actually discloses media in which animal proteins are used, and that their use of the term "may be" is used throughout the disclosure "ambiguously throughout the disclosure, more specifically, even for the key aspect of the disclosure" (page 10). Applicants then point to sections of the disclosure of Price et al. where animal proteins and components are listed that may be used in the medium. However, it is clear from the disclosure of Price et al., that they do not intend that all of the numerous components listed should be added to culture medium. There are at least 3 pages of lists of components that "may be" used in the media. However, it is maintained that at page 4-5 of Price et al., it is disclosed that the plant extracts, including soy and yeast hydrolysates, are useful for replacing all components of animals in culture medium. Price discloses that "the use of such animal-derived supplements in cell culture media, however, also has certain drawbacks...There remains a need for a serum-free, low-protein culture medium suitable for cultivation of animal cells, which is completely devoid of animal or human proteins. Such a medium formulation...will eliminate the risk of the introduction of adventitious animal and human pathogens. The current invention provides such an animal cell culture medium formulation" (page 6). Furthermore, at page 22, it is disclosed "the present invention also relates to methods for replacing or substituting animal-derived products with plant

peptides, plant lipids, plant fatty acids, and/or enzymatic digests or extracts of yeast cells (or combinations thereof). Such plant and/or yeast-derived nutrients may be substituted for any number of animal-derived culture medium components or substituents, including but not limited to blood-derived products, tissue/organ/gland extracts, animal-derived fatty acids and lipids, sterols, and lipoproteins" and goes on to disclose typical animal components that are replaced using the disclosed extracts. Therefore, it is clear that the reference teaches the replacement of animal products in culture media by the disclosed plant and yeast hydrolysates.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nancy T. Vogel whose telephone number is (571) 272-0780. The examiner can normally be reached on 7:00 - 3:30, Monday - Friday.


If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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NV
1/14/08


NANCY VOGEL
PRIMARY EXAMINER